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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,334	01/16/2004	Steven C. Pruitt	03551.0149	7276

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EXAMINER	
LONG, SCOTT	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,334	PRUITT ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 1/16/2004.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 5/2004 & 7/2006.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-21 are pending. Claims 1-21 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The new oath or declaration, having the signatures of all inventors, received on 10 June 2004 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 21 May 2004 and 11 July 2006 consisting of 4 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from provisional U.S. Application No. 60/440,510 filed 01/16/2003. The instant application has been granted the benefit date, 16 January 2003, from the application 60/440,510.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 recites the limitation "the fluorescent reporter" in step a). There is insufficient antecedent basis for this limitation in the claim.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Claims 1, step c) and 12, step c) recite "integrating into the genome...a recombinase". The omitted elements are: From reading the specification, the examiner believes that a "recombinase gene" has been integrated into the genome and not that a recombinase protein was packaged along with the vector. This should be clarified in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088).

Claim 1 is directed to a method for identifying genes expressed during differentiation of a cell comprising the steps of: a) integrating into a site in the genome of a host cell, a cell lineage targeting vector comprising, a pair of recombinase recognition sites flanking one or more polyadenylation sites, a first selectable marker placed downstream of or between the two recombinase recognition sites, a reporter gene placed downstream of the recombinase recognition sites, and a cell lineage specific gene promoter placed upstream of the recombinase recognition sites or a cell specific lineage gene placed downstream of the recombinase recognition sites, b) amplifying cells generated from the host cell; c) integrating into the genome of a plurality of the amplified cells, a gene-trap vector comprising a splice acceptor, a type IIS restriction endonuclease cleavage site, a recombinase, one or more polyadenylation sites, a second selectable marker and a splice donor; d) allowing the cells to differentiate; e) isolating cells in which the reporter gene is expressed indicating expression of the cell lineage specific gene; f) identifying trapped genes in the isolated cells. Thorey et al.

teach, "a strategy employing gene trap...and site-specific recombination (Cre.loxP) has been used to identify genes that are transiently expressed during...development. Thorey et al. teach diagrams (Fig.1, page 3082), that show a system of two vectors. One of the vectors comprises a pair of recombinase recognition sites (loxP) flanking one polyadenylation site, a selectable marker (Neo) placed between the recombination sites, a reporter gene (lacZ) downstream of the recombination sites. The other vector comprises cellular promoter and a trapped gene flanked by recombination recognition sites (Cre). Thorey et al. describe isolating cells derived using their system (pages 3082-3083). Thorey et al. teach, that their system is "useful for demarcating cell lineages and for tracking cell fate and migration in the developing embryo." (page 3087).

Claim 2 is directed to the method of claim 1 wherein the trapped genes are sequenced. Thorey et al. teach sequencing of genes, using plasmids (concatamers).

Claim 3 is directed to the method of claim 2, wherein inverse PCR is used. Thorey et al. teach "inverse PCR" (page 3082).

Claim 4 is directed to the method of claim 2, wherein RT-PCR is used. Thorey et al. utilize rapid amplification of cDNA ends (RACE). Accordingly, the cDNA was derived from RNA and needed to be reverse transcribed.

Claim 5 is directed to the method of claim 1, wherein the step of identifying the trapped genes in step f) comprises the steps of: a) preparing mRNA from cells in which the fluorescent reporter is expressed in d); b) synthesizing a first and second cDNA strands from the mRNA; c) digesting with type IIS restriction endonucleases to produce Assay Tags wherein each Assay Tag comprises a portion of a trapped gene and a

portion of the gene-trap vector; d) concatenating the Assay Tags; e) amplifying and sequencing the concatamers to identify the sequence of the portion of the trapped gene. Thorey et al. teach, selection of clones, isolation of cellular RNA, followed by RACE (page 3084, footnotes of Table 1). These steps comprise the sequence strategy of Thorey et al. According to Thorey et al. "all sequences showed typical cell DNA-provirus junctions" (page 3085), indicating that the region sequenced contained both the trapped sequence and the gene-trap vector.

Claim 10 is directed to the method of claim 1, wherein the recombinase is Cre or FLP. Thorey et al. teach Cre recombinase.

Accordingly, Thorey et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088) in view of Zambrowicz et al. (Int.J.Dev.Biol. 1998; 42: 1025-1036) and further in view of Velculescu et al. (Science. 20 October 1995: 484-487).

The claimed invention is directed to a method for identifying genes expressed during differentiation of a cell comprising the steps of: a) integrating into a site in the genome of a host cell, a cell lineage targeting vector comprising, a pair of recombinase recognition sites flanking one or more polyadenylation sites, a first selectable marker placed downstream of or between the two recombinase recognition sites, a reporter gene placed downstream of the recombinase recognition sites, and a cell lineage specific gene promoter placed upstream of the recombinase recognition sites or a cell specific lineage gene placed downstream of the recombinase recognition sites, b) amplifying cells generated from the host cell; c) integrating into the genome of a plurality of the amplified cells, a gene-trap vector comprising a splice acceptor, a type IIS restriction endonuclease cleavage site, a recombinase, one or more polyadenylation sites, a second selectable marker and a splice donor; d) allowing the cells to differentiate; e) isolating cells in which the reporter gene is expressed indicating

expression of the cell lineage specific gene; f) identifying trapped genes in the isolated cells. The claimed invention also incorporates elements of modified serial analysis of gene expression (SAGE), particularly type IIS endonuclease sites and Assay Tags.

The teachings of Thorey et al. are described above in the 35 USC 102 section.

Thorey et al. does not specifically teach use of the SAGE technique with gene trapping.

Zambrowicz et al teach however, teach the use of SAGE with gene trapping techniques (page 1026). Zambrowicz et al. discuss the usefulness of combining gene trap and SAGE techniques for "high through-put methods...used for studying expression patterns of large numbers of genes at the RNA [level]." (page 1026) In particular, Zambrowicz et al. describe the utility of gene traps for identifying genes expressed during differentiation. Zambrowicz et al. also teach alternative selection techniques comprising the use of thymidine kinase fusion proteins (page 1030, col.1), satisfying the claim limitations of claims 11 and 21.

The details of SAGE are discussed in Velculescu et al., including the use of type II restriction sites and assay tags. Velculescu et al. also teach biotinylated DNA, as per the limitations of claims 6 and 16.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the use of gene traps and serial analysis of gene expression. In addition, a skilled artisan would find it obvious to utilize an enhanced green fluorescent protein (as in claims 8-9 and 18-19) as a functional equivalent of β-galactosidase in the systems described by Thorey and Zambrowicz

The person of ordinary skill in the art would have been motivated to make those modifications because "gene trapping combined with methods to monitor induction of expression of the trapped gene have now been used in a variety of cell types" (Zambrowicz, page 1030) and Zambrowicz et al. suggest combining gene trap and SAGE techniques for "high through-put methods...used for studying expression patterns of large numbers of genes at the RNA [level]." (page 1026). Furthermore, combining high throughput screening elements with gene trapping vectors is merely "making integral" the two known processes; the MPEP 2144.04 holds that this type of combination is obvious. The person of ordinary skill in the art would have been motivated to make those modifications because fluorescent proteins, such as Green Fluorescent Protein (GFP) are functionally equivalent to lacZ (β-galactosidase) systems and do not require further reagents, such as X-gal, for visualization, as is the case for β-galactosidase.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Thorey and Zambrowicz and Velculescu because each of these teachings generated successful results independently and there is no indication that the combinations of high throughput screening elements with gene trapping vectors would be unsuccessful.

Therefore the method as taught by Thorey et al. in view of Zambrowicz et al. and further in view of Velculescu et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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